REMARKS

Specification Amendments

The specification has been amended to inactivate a hyperlink, as requested by the Examiner.

Claim Amendments

Claims 1-16, 29, and 31 are now pending in the application. Claims 1, 3-6, 8, 12, 29, and 31 have been amended and claim 7 has been cancelled. Claims 36-45 are new.

Support for claim 36 can be found, for example, at page 6, line 16, to page 7, line 4. Support for claim 37 can be found, for example, at page 8, lines 4-7. Support for claims 38-39 can be found, for example, page 8, lines 6-8. Support for claim 40 can be found, for example, at page 8, lines 8-10. Support for claim 41 can be found, for example, at page 8, lines 10-14. Support for claim 42 can be found, for example, at page 8, lines 14-17. Support for claim 43 can be found, for example, at page 8, lines 18-21. Support for claim 44 can be found, for example, at page 9, line 20 to page 10, line 2. Support for claim 45 can be found, for example, at page 10, lines 2-10.

No new matter has been added. Reconsideration and reexamination are respectfully requested in view of the amendments and the following remarks.

Objections

The Examiner objected that the disclosure contains an embedded hyperlink and/or other form of browser-executable code. The applicants have amended the specification to inactivate the link, as per MPEP § 608.01. The applicants submit that the disclosure is now proper.

Withdrawal of the objection is requested.

Non-Statutory Subject Matter Under 35 U.S.C. § 101

The Examiner has rejected claims 1-16, 29, and 31 as allegedly directed to non-statutory algorithm type subject matter. The applicants respectfully disagree.

Algorithm-type subject matter is patentable if the claims represent a "useful, concrete and tangible result". *State Street Bank & Trust co. v. Signature Financial Group Inc.,* 149 F.3d 1368, 1378 (Fed. Cir. 1998). As amended, independent claims 1 and 31 "output[] selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands." The binding energies that are outputted by the claimed methods are a useful, concrete and tangible result because they represent the predicted binding conformations of the set of ligands, as clarified by the amendment, and also because they provide a basis for evaluating the ligands in their predicted binding conformations.

The basis for evaluating the predicting binding conformations of the ligands is the binding energies. Ligands having low binding energies are more likely to bind in nature than ligands having higher binding energies. The outputted binding energies therefore make it possible, for example, to identify or distinguish ligands that are likely to bind with the predicted conformation to the identified binding region of the protein. This is a very useful, concrete, and tangible result. For example, determining which ligands are likely to bind to a particular protein, and how and where they bind, can facilitate research on protein function and enable the design of new drugs.

For at least these reasons, the applicants submit that the amended claims are properly directed to patentable subject matter. Withdrawal of the rejection is requested.

Indefiniteness Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1, 29, 31 on the alleged grounds that "preferred binding conformations" causes the claims to be vague and indefinite because it is unclear what criteria are being used to consider a conformation to be a "preferred binding conformation".

The applicants have amended claims 1 and 31 to indicate that the preferred binding conformations are "determined by generating and ranking initial conformations for each ligand in the set of ligands at the binding region using docking techniques". For example, conformations can be ranked using an energy scoring function (Specification page 28, lines 9-11; page 34, lines 5-9; page 38, lines 11-16; page 40, lines 14-18) or using the percentage of ligand

surface area buried in a protein (Specification page 17, lines 1-3; page 38, lines 11-16). The applicants submit that, as amended, claims 1 and 31 are proper and definite.

The Examiner rejected claims 4-8 on the alleged grounds that "best conformations" causes the claims to be vague and indefinite because it is unclear what criteria are being used to consider a conformation to be the "best conformation". The applicants have amended claim 4 to indicate that "a preliminary energy function" is scored "for at least some of the initial conformations" and the best conformations are selected from the initial conformations "based at least in part on the preliminary energy scores". The applicants submit that, as amended, claims 1 and 31 are proper and definite.

Withdrawal of the rejections is requested.

Lack of Enablement Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1-16, 29, and 31 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner acknowledges that the specification discloses information sufficient to practice the claimed method based on crystal structures of the proteins described as examples. But the Examiner says that it would be unpredictable for one to practice the claimed invention with any other protein because protein crystallization is unpredictable. The applicants respectfully disagree.

Claims 1, 29, and 31 require "provid[ing] structural information describing the structure of a protein and a set of one or more ligands" and "using the structural information for the protein to identify a binding region of the protein". Such structural information can be obtained from crystallographic studies, as demonstrated in Examples 1 and 2 for the protein t-RNA synthetase (Specification page 27, lines 12-13, and page 30, lines 18-22) and Example 5 for the protein bovine rhodopsin (page 40, lines 5-9). Such structural information can also be obtained from other sources, for example, from computational models (Specification page 16, lines 1-7). Indeed, Examples 3 and 4 describe docking studies for OR S25 and OR S18, for which no x-ray crystallographic data was available, starting from a predicted structure as described in co-

pending U.S. Application Serial No. 09/816,755 (Specification page 31, lines 4-6; page 33, lines 4-9; page 38, lines 4-7).

Thus, while crystallographic data can be used to practice the invention, obtaining crystallographic structural information is clearly not required by the language of the claims. For this reason, and also because reliable alternative methods for obtaining the required structural information are described in the specification, any unpredictability in the ability to crystallize a particular protein does not render the claimed methods non-enabled. Accordingly, the applicants respectfully submit that the claimed methods are fully enabled.

The evidence as a whole, as demonstrated by a consideration of the Wands factors, clearly supports this conclusion. *In re Wands*, 858 F.2d 731, 737, 740 (Fed. Cir. 1988). First, the quantity of experimentation need to practice the invention is very small, as the molecular dynamics simulations upon which the invention relies are fully operational and generally known to those of skill in the art. Second, the amount of direction presented in the specification is fully adequate to enable one of skill in the art to practice the invention because the specification clearly describes how these known simulations are used to implement the invention. Third, the applicants include five complete and distinct working examples.

Fourth, the nature of the invention is not experimental laboratory biology but rather computer-implemented modeling, in particular, models of molecular dynamics. Such methods are reliably implemented to yield definite results. Fifth, the prior art is well developed and very sophisticated, as indicated for example by the references in the specification. Sixth and similarly, the relative skill of those in the art is quite high. Such persons are knowledgeable of computer coding techniques, mathematical methods, and protein structure and function. Seventh and as suggested above, the art of computer modeling is not an unpredictable science but, rather, a very deterministic one.

Eighth and finally, the breadth of the claims are consistent with and fully supported by the specification. Thus, the evidence as a whole indicates that it would not require undue experimentation to practice the claimed invention. Accordingly, the applicants respectfully

submit that the claimed methods are fully enabled by the specification, and should not be limited in scope to the examples described in the specifications. Withdrawal of the rejection is requested.

Claim Rejections 35 USC § 102

The Examiner rejected claims 1, 29, and 31 under 35 U.S.C. § 102(a) as allegedly unpatentable over Zou et al. 1999 ("Zou"). The applicants respectfully disagree.

Zou describes the use of the well-known Generalized-Born (GB/SA) model of solvation to estimate ligand binding energies. Zou modifies the GB/SA model to account for electrostatic interactions between the ligand and the solvent, introduces a formula to estimate the binding free energy, and then calculates a free energy score for each conformation of one or more ligands. The resulting scores are used to rank ligands or their conformations, and to explore appropriate parameters for the model.

In contrast, the claimed invention provides a hierarchical method for modeling ligand-protein binding interactions. After identifying a binding region, the claimed invention models initial conformations of one or more ligands using docking techniques, and identifies preferred binding conformations for each ligand at the binding region. Then, the preferred conformations are optimized using annealing molecular dynamics that include solvation effects. The conformation of each ligand that has the lowest binding energy is selected and the binding energy is outputted to the researcher.

Thus, whereas Zou uses a single model to rank ligands or conformations, the claimed invention first uses docking techniques to identify preferred conformations and then uses annealing molecular dynamics including solvation effects to optimize those preferred configurations.

The hierarchical nature of the claimed invention provides an efficient and accurate method for selecting a binding conformation of a ligand and producing data to evaluate the ligand. The exhaustive methods of Zou are computationally demanding, and Zou precalculates certain quantities and cuts-off calculation of others in order to implement these methods (page 8036, section 5). In contrast, the claimed invention can use efficient coarse-grained methods to

first model initial conformations of ligands and identify preferred binding conformations, and computationally intensive and accurate fine-grained methods to then optimize each of the preferred conformations and select the best one – i.e. the one having the lowest energy score.

For any and all of these reasons, the applicants respectfully submit that claims 1, 29, and 31 are allowable. Claims 2-16 and new claims 36-45 depend from claims 1 and 31 respectively, and are allowable at least for any of the reasons given for claims 1 and 31. Withdrawal of the rejection is requested.

In summary, reconsideration and withdrawal of the Examiner's objections and rejections are respectfully requested. Early allowance of the claims of this application is earnestly solicited.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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